

### **REMARKS**

Claims 1-47 are pending in this application. Claims 2-5, 23-28, 30-35 and 43 have been withdrawn from consideration. No claims stand objected to. The Applicants herein cancel Claims 7, 8, and 21 without prejudice or disclaimer to the subject matter contained therein. In addition, the Applicants herein amend Claims 1, 6, 9, 22, 36, 37, 41, and 42. The claims, as amended, find support at pages 17-20, and pages 32-36 of the instant specification.

### **SPECIFICATION OBJECTIONS**

The disclosure (page 7, line 4) stands objected to because it contains an embedded hyperlink. In response to this objection, the Applicants amended this portion of the specification to remove this embedded hyperlink. Therefore, this objection is now moot and should be withdrawn.

### **CLAIM OBJECTIONS**

Claims 21 and 22 stand objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claims. The Applicants herein cancel Claim 21, and amend Claim 22 to make it independent. Therefore, both of these claim objections are now moot.

### **CLAIM REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH**

Claims 7-22, 29, 37-42, and 44-47 stand rejected under 35 U.S.C. § 112, first paragraph, because the Examiner alleges that the specification, while being enabling for a human IL-18 (SEQ ID NO:1) PEGylated at C38 and/or C68 and the human IL-18 mutant (SEQ ID NO:8) PEGylated at residue D157C, does not reasonably provide enablement for the other claimed human IL-18 PEGylated proteins and mutants. In response to this rejection, the Applicants herein cancel Claims 7, 8, 21, and 41, and amend Claims 9, 22, 37, and 42. As amended, the instantly pending claims now only recite human IL-18 (SEQ ID NO:1) PEGylated at C38 and/or C68 and the human IL-18 mutant (SEQ ID NO:8) PEGylated at residue D157C. In view of these amendments, the Applicants respectfully request reconsideration and withdrawal of Claims 9-20, 38-40, 42, and 44-47 under 35 U.S.C. § 112, first paragraph.

**CLAIM REJECTIONS UNDER 35 U.S.C. § 112 , SECOND PARAGRAPH**

Claims 7-10 stand rejected under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention. Specifically, the Examiner opines that the recitation, “biologically active composition”, in these claims renders them indefinite. In response, the Applicants herein cancel Claims 7 and 8 without prejudice or disclaimer, and amend Claim 9 (and dependent Claim 10) to recite “[a] composition”, thereby omitting the words “biologically active” from these claims.

Claim 1 stands rejected under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite. Specifically, the Examiner indicates that there is a word missing in this claim between the words, “group” and “of”. In response, the Applicants herein amend Claim 1 to recite the phrase, “the group consisting of”.

Claim 6 stands rejected under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite. Specifically, the Examiner objects to the word, “contains” in this claim. In response, the Applicants herein amend Claim 6 to replace the word “contains” with the word, “comprises”.

In view of the forgoing amendments, the Applicants submit that 1, 6, 9, and 10 are definite. Accordingly, the Applicants respectfully request reconsideration and withdrawal of the rejections of Claims 1, 6, 9, and 10 under 35 U.S.C. § 112, second paragraph.

**CLAIM REJECTIONS UNDER 35 U.S.C. § 102**

Claim 1 stands rejected under 35 U.S.C. § 102(b), as allegedly anticipated by Yamamoto, *et al.* (EP 845530 A3). The Examiner points out that Yamamoto, *et al.* teaches a human IL-18 substitution mutant comprising from one to five amino acid substitutions in the sequence of the instant SEQ ID NO:1, specifically a mutant that comprises a cysteine at residue 38 and the cysteine at residue 68.

In response to this rejection, the Applicants herein amend Claim 1 to replace the phrase, “said substitution being from one to five amino acid residues...” with the phrase, “said substitution being from three to five amino acid residues...” A single prior art reference anticipates a claimed invention only if it identically shows every element of the claimed invention. *In re Bond*, 15 U.S.P.Q.2d 1566 (Fed. Cir. 1990). Because

Yamamoto does not teach an IL-18 substitution with three to five of the recited substitutions recited in Claim 1, it does not anticipate Claim 1 under *In re Bond*. In view of this amendment, the Applicants request reconsideration and withdrawal of the rejection of Claim 1 under 35 U.S.C. § 102(b).

Claims 7 and 8 stand rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Tamarkin, *et al.* (US Patent 6,274,552). The Applicants herein cancel Claims 7 and 8 without prejudice or disclaimer, thereby rendering these rejections moot.

Claims 7, 8, 36, 39, 41, and 44 stand rejected under 35 U.S.C. § 102(e) as being allegedly anticipated by Burton, *et al.* (US 2004/0136992). The Applicants herein cancel Claims 7, 8, \*\* without prejudice or disclaimer. In addition, the Applicants herein amend Claim 36 to add a limitation about which two amino acid residues of human IL-18 (SEQ ID NO:1) are conjugated to the water-soluble polymer. Burton, *et al.* is silent with respect to where on the IL-18 polypeptide the water-soluble polymer should be attached. Because Burton, *et al.* does not identically disclose every element of Claim 36, as amended, it does not anticipate Claim 36, as amended. In view of the forgoing remarks and claim amendments, the Applicants respectfully request reconsideration and withdrawal of the rejections of Claims 1 and 36, as amended, under 35 U.S.C. §§ 102(b) and 102(e).

### **CLAIM REJECTIONS UNDER 35 U.S.C. § 103**

Claims 36-40 stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Burton, *et al.*, *supra* in view of Martinez, *et al.* (US 2004/0062746 A1) in further view of Benjamin, *et al.* (*Ann. Rev. Immune* 2: 67-101 (1984)). According to the Examiner, Burton, *et al.* teaches a composition and method of preparing a biologically active composition comprising human IL-18 and covalent derivatives prepared by linking chemical moieties, such as PEG, to functional groups. She also points out that Burton, *et al.* teaches IL-18 amino acid substitution mutants, including cysteine mutants, and inactivation of N-glycosylation sites. The Examiner also alleges that Martinez, *et al.* teaches conjugation of polyalkylene glycols, specifically PEG and mPEG, to IL018. According to the Examiner, Benjamin, *et al.* teaches that the surface of proteins consist of a complex array of overlapping potential antigenic determinants.

The Examiner contends that it would have been *prima facie* obvious to the skilled artisan, at the time the instant invention was made, to combine the teachings of Burton, *et*

*al.* with the teachings of Martinez, *et al.*, because Burton, *et al.* teach that IL-18 derivatives can be conjugated with polymer moieties and Martinez, *et al.* teaches that numerous polymers are suitable for conjugating purposes. Further, Benjamin, *et al.* teaches the surface of any protein consists of overlapping antigenic determinants. She argues that the skilled artisan would have reasonably expected success because, “although the claimed method steps of contacting of the claimed IL-18 substitution mutant polypeptide with a water-soluble polymer would not necessarily produce biologically active PEGylated polypeptide, the PEGylated polypeptide would be comprised within a biologically active composition because of the antigenic response that would be achieved by administering the PEGylated polypeptide *in vivo*.” (Office Action at the paragraph bridging pages 11 and 12.) The Examiner notes that the claims, as filed, do not provide any limitation regarding where the PEG should be conjugated to the IL-18 polypeptide.

The Applicants herein amend Claims 36 and 37 (and dependent Claims 38-40 to add limitations about which residues of the IL-18 polypeptides are conjugated to the water-soluble polymer. As the Applicants show, in Example 2, Tables 1A and 1B in the instant application (pages 17-30), that the residues at which the IL-18 and IL-18 mutants are PEGylated, affect the biological potencies of the polypeptides. Burton, *et al.*, Martinez, *et al.*, and Benjamin, *et al.* neither teach nor suggest, either individually, or in combination, site-specific PEGylation of native IL-18 (SEQ ID NO:1) or the IL-18 substitution mutant of SEQ ID NO:8. Therefore, Claims 36-40, as amended, are patentable over Burton, *et al.*, Martinez, *et al.*, and Benjamin, *et al.*

Claims 41, 42, and 44-47 stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Burton, *et al.*, *supra*, in view of Martinez, *et al.*, *supra*, in further view of Kim, *et al.* (*J. Biol. Chem.* 277(13): 10998-11003 (2002)). The Examiner’s views of the teachings of Burton, *et al.* and Martinez, *et al.* are discussed above. She posits that Kim, *et al.* teaches that IL-18 binds and neutralizes IL-18P biological activity. Also, according to the Examiner, Kim, *et al.* teaches “that E42 and K89 of wild-type human IL-18 (SEQ ID NO:1) are critical amino acid residues for the integrity of IL-18 structure and are important for binding to cell surface receptors, for signal transduction, and for neutralization by IL-18BP . . . .” (Office Action at page 13, first full paragraph.) The Examiner argues that it would have been *prima facie* obvious to the skilled artisan, at the time the instant invention was made, to combine the teachings of

Burton, *et al.* with the teachings of Martinez, *et al.*, because Burton, *et al.* teaches that IL-18 derivatives can be conjugated with polymer moieties, and Martinez, *et al.* teaches that numerous polymers are suitable for conjugating to polypeptides. The Examiner the concludes that the skilled artisan would have reasonably expected success, because Burton, *et al.* teaches improved pharmacokinetics and subcutaneous bioavailability in proteins, including IL-18, that are conjugated to water-soluble polymers. She also argues that, “[b]ecause Kim *et al.* teach that E42 and K89 of wild-type IL-18 are critical to IL-18BP binding, any steric interference with the ability of IL-18BP to bind, near E42 and/or K89 will result in reduced IL-18BP.” (Office Action, at second full paragraph on page 13.)

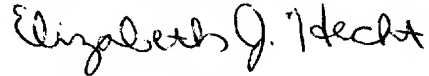
The Applicants herein amend Claims 41 and 42 (and dependent Claims 44-47) to add limitations about where the human IL-18 (SEQ ID NO:1) and IL-18 substitution mutant (SEQ ID NO:8) are conjugated to the water-soluble polymer. Burton, *et al.*, Martinez, *et al.*, and Kim, *et al.* neither teach nor suggest, either individually, or in combination, site-specific PEGylation of native IL-18 (SEQ ID NO:1) or the IL-18 substitution mutant of SEQ ID NO:8. Therefore, Claims 36-40, as amended, are patentable over Burton, *et al.*, Martinez, *et al.*, and Kim, *et al.* In view of the forgoing remarks and claim amendments, the Applicants respectfully request reconsideration and withdrawal of the rejections of Claims 36-42, and 44-47, as amended, under 35 U.S.C. § 103(a).

The Applicants reserve the right to prosecute, in one or more patent applications, the claims as originally filed, the cancelled claims, the withdrawn claims, and any other claim that is supported by the instant specification. In view of the foregoing amendments and remarks, the Applicants respectfully submit that the subject application is in condition for allowance. If the Examiner has any remaining

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objections or concerns, the Applicants invite her to contact the Applicants' undersigned attorney at the below telephone number to resolve such issues and advance the case to issue.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Elizabeth J. Hecht". The signature is fluid and cursive, with the first name being the most prominent.

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